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EFFICACY OF ALIROCUMAB IN 1,191 PATIENTS WITH A WIDE SPECTRUM OF MUTATIONS IN GENES CAUSATIVE FOR FAMILIAL HYPERCHOLESTEROLEMIA

Moderated Poster Contributions
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Background: Next Generation Sequencing was performed to examine treatment response with alirocumab in patients carrying one or more causative mutation(s) in five familial hypercholesterolemia (FH) genes.

Methods: From 6 clinical trials of alirocumab (one Phase 2, five Phase 3), 1191 patients with elevated LDL-C and phenotypic FH (including 758 treated with alirocumab) were sequenced for mutations using the SEQPRO LIPO platform in LDL receptor (LDLR), apolipoprotein B (APOB), PCSK9 (PCSK9), LDL receptor adaptor protein 1 (LDLRAP1), and signal-transducing adaptor protein 1 (STAP1) genes. New mutations were confirmed by Sanger sequencing and MLPA analysis in case of large gene rearrangements in the original DNA samples.

Results: In total, 387 patients (32%) and 438 (37%) had single receptor defective and receptor negative mutations in LDLR, respectively; 46 (4%) had single mutations in APOB; 8 (0.7%) had single gain-of-function mutations in PCSK9; 2 (0.17%) were homozygous for mutations in LDRAP1; 6 (0.5%) were double heterozygotes for mutations in both APOB and LDLR; 10 (0.8%) were compound heterozygotes in LDLR; 1 (0.08%) was a double heterozygote for mutations in LDLR and PCSK9; 293 (25%) had no identifiable causative mutation in any of the genes investigated. LDL-C reduction with alirocumab at week 12 was generally similar across background FH mutations: LDLR defective heterozygotes -51.8% (N=231), LDLR negative heterozygotes -50.2% (N=289); APOB heterozygotes -45.5% (N=26); PCSK9 heterozygotes -53.3% (N=5); subjects with no identifiable mutation -51.0% (N=171). A similar large decrease in LDL-C was also seen in the 3 double heterozygotes (LDLR, APOB, -49.2%) and 6 potentially compound heterozygous (LDLR, -48.0%) patients. Overall rates of TEAEs were similar for alirocumab vs controls, with a higher rate of injection site reactions with alirocumab.

Conclusions: In this large cohort of FH patients, individuals with a wide spectrum of mutations in genes causative for FH responded substantially to alirocumab treatment. LDL-C-lowering activity by alirocumab in compound heterozygotes and double heterozygotes is likely attributable to the presence of at least one partially functional allele.